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Effects of Oral Contraceptive Usage on B12 and Folate Levels

SUMMARY

Evidence shows a fall in folate and vitamin B_{12} levels in women taking oral contraceptives. These levels do not return to normal until about three months after usage has stopped, but many women become pregnant during this time. This paper examines the evidence for an effect on such pregnancies of lowered folate and B_{12} levels, and concludes that nutritional counselling should begin in schools, should continue in the medical care of women in their childbearing years, and folic acid supplementation should begin as soon as pregnancy is confirmed. This supplementation should be periconceptional in women at higher risk of bearing a child with neural tube defects, and greater in multiple pregnancy, malabsorption, hemolytic anemia and concomitant use of drugs known to be folate antogonists. (Can Fam Physician 1985; 31:1523-1525.)

SOMMAIRE

L'évidence accumulée révèle une diminution des niveaux de folate et de vitamine B_{12} chez les femmes qui prennent des anovulants. Ces niveaux ne reviennent pas à la normale avant qu'il ne se soit écoulé trois mois après la cessation des anovulants, mais bien des femmes deviennent enceintes durant cette période. Cet article examine les preuves d'un tel effet sur les grossesses où les niveaux de folate et de B_{12} sont diminués, et conclut que le counselling nutritionnel devrait débuter dans les écoles, se poursuivre au niveau des soins médicaux aux femmes en âge de procréer, et qu'un supplément d'acide folique devrait être initié dès la confirmation de la grossesse. Ce supplément devrait être plus important chez les femmes à haut risque de porter un enfant souffrant d'anomalie du tube neural, de grossesses multiples, de malabsorption, d'anémie hémolytique et faisant un usage concomitant de médicaments connus comme antagonistes du folate.

Key words: Oral contraceptives, vitamin B_{12}, serum folate

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THERE ARE NOW many reports of a fall in folate and vitamin B_{12} levels in women taking contraceptive agents (OCs). With a normal diet, folate levels return to normal about three months after discontinuing OCs.[1] Should a pregnancy ensue within six months of discontinuing OCs, there is a greater incidence of folate deficiency during the pregnancy than in those who had not taken OCs before becoming pregnant.[2]

In my practice many women become pregnant within three months of discontinuing the use of these drugs, despite advice to the contrary. This paper reviews the possible effects of oral contraceptives on vitamin B_{12} and folate levels, and discusses the attendant risks to the mother and the fetus if these vitamin levels drop and a pregnancy ensues before they are rectified.

Folate Levels in OC Users

There are many reports of an association between folate deficiency and the use of OCs[3-5] Shojania[5] showed that folate levels fell progressively with duration of OC usage. However, Castren[6] and Paine,[7] found no change in folate levels with time on steroid contraceptives. These findings, however, were not confirmed by others;[7-9] in fact, Castren and Rossi[6] reported a slight increase in the average folic acid level of 15 of 30 women after three months' treatment with OCs. I similarly found a rise in folic acid levels in OC users under age 25 (unpublished observations).

Clinical Effects of Low Folate Levels in The Non-pregnant Woman

Anemia

There are now several reports of megaloblastic anemia in users of contraceptive steroids.[3, 4, 10-12]

Pregnancy predisposes to folate deficiency; Chanarin[14] reported folic acid deficiency anemia in $2.1 \pm 1.5\%$ of pregnancy in Britain, Eire, and Canada. Therefore, women who embark on a pregnancy soon after discontinuing OCs are likely at greater risk of folate deficiency and its complications.[15] Martinez and Roe[16] verified that women becoming pregnant within six months of discontinuing OCs had lower levels of serum and red blood cell folate than those who had not been taking birth control pills shortly before becoming pregnant.

Cervical Dysplasia

In 1973, Whitehead et al.[17] observed megaloblastic features in cervi-

cal epithelial cells from a group of women using OCs. These women had no associated evidence of systemic folate deficiency, but the cytological changes were reversed with oral folate supplementation.

Butterworth et al.[18] showed that mean RBC folate concentration was lower among OC users than non-users (189 versus 269 ng/ml respectively, $p<0.01$) and even lower among users with dysplasia (161 versus 269 ng/ml respectively, $p<0.001$). They suggest that either a reversible localized derangement in folate metabolism may sometimes be misdiagnosed as cervical dysplasia, or such a derangement is an integral component of the dysplastic process and may be arrested, or possibly reversed, by folic acid supplementation.

Dental caries and dermatological evidence of malnutrition

Prasad et al.[19] showed a decrease in serum folate and erythrocyte folate due to OCAs, mainly in an upper socioeconomic group of subjects. There was also an increase in abnormal clinical findings, indicating malnutrition, such as angular lesions of the mouth, dry skin and dry hair compared with a control group not taking OCs. The incidence of dental caries was increased in OC users in a higher socioeconomic group. These latter effects might be caused by a decreased plasma zinc concentration.[20]

Mental function

In 1962 Herbert[21] suggested that mental changes were a part of the clinical folate deficiency state.

Thornton[22] demonstrated that hospitalized psychiatric patients have a higher prevalence of subnormal serum folate levels than do normal controls, regardless of sex or age. Further, the dietary ratings of the low serum folate patients did not differ from the normal folate level patients, so some other factor than diet must be at work.

Postpartum psychosis

Thornton[23] also describes the case of a young woman given no folate supplementation during pregnancy and who developed severe postpartum psychosis. She was found to have a macrocytic anemia with undetectable serum folate. Treatment with intramuscular folic acid was begun, and on the tenth day of therapy, a complete remission occurred. There have however, been no other similar case reports.

Thus lowered folate levels associated with OC usage have been implicated in the etiology of megaloblastic anemia, cervical dysplasia, dental caries and several dermatological conditions. It seems unlikely, however, that any folate lowering due to the use of contraceptive steroids has resulted in clinical psychosis.

Clinical Effects of Low Folate Levels in Pregnant Women

There are many reports of complications from low folic acid levels in both mother and fetus. This lowered vitamin level could be due to a pregnancy beginning very soon after discontinuing OCs,[16] the effects of the pregnancy itself on maternal folate levels,[13, 14] celiac disease in the mother, or maternal use of other drugs known to lower folate levels such as diphenylhydantoin, alcohol, barbiturates, colchicine and numerous drugs used in cancer chemotherapy.[24]

Hazards to the mother and fetus in the absence of frank anemia are controversial but include the following:

Restless leg syndrome

Botez[25] has suggested a correlation between this syndrome in pregnancy and folate deficiency.

Hydatidiform mole

Reynolds[26] advances the thesis that hydatidiform mole may be partly due to folate deficiency.

Toxemia of pregnancy

In 1967 Stone[27] and coworkers implicated folate deficiency in toxemia of pregnancy.

Late pregnancy bleeding

That bleeding late in a pregnancy may be partly due to low folate levels has been postulated by Streiff.[28]

Abortion, recurrent abortion and abruptio placentae

Hibbard and others[29-31] have suggested that low folate levels are at least partly responsible for some abortions and abruptio placentae. This work, however, has been discredited because they used the formiminoglutamic acid test (FIGLU) for folate, which is not specific enough.

Folate deficiency in the newborn

In a study of 100 women at risk for nutritional deficiencies, Blot et al.[32] found that though there was no difference in hemoglobin and RBC indices between infants born of iron or folate deficient mothers and others, there was a significant correlation between mother and newborn serum folate ($p<0.001$) and RBC folate values ($p<0.001$).

Neural tube defects (NTDs)

Smithells and associates[33] found that first trimester RBC folates and WBC vitamin C levels were significantly lower in six mothers who gave birth to infants with NTDs when compared to controls. This same group were able to reduce an expected incidence of recurrence of NTD in infants from 5% to 0.6% by giving mothers planning a pregnancy a prophylactic preparation containing folic acid. Further, in mothers who had already given birth to more than one affected child, the expected recurrence rate of 11.5% was reduced to zero.[34] There are similar studies by Laurence and coworkers.[35-37] However, these trials were very small and the effect of diet and other ingested vitamins cannot be excluded from the folate effect. Both Smithells and Laurence have recommended larger trials.

Other congenital defects

Folate deficiency has been implicated in other fetal malformations.[38, 39] In a study by Blot,[32] the mothers of two infants with hare lip and cardiopathy exhibited low folates and low ferritin values. Other workers have been unable to demonstrate any relationship between malformations and folate deficiency.[40-42]

Mental retardation

The evidence relating folate deficiency in pregnancy to mental retardation and other defects in the central nervous system function and development is reviewed by Herbert and Tisman.[43]

Small for dates (retarded fetal growth)

Elliot[44] related retarded fetal growth to maternal folate deficiency. In a

prospective study of 805 women seen early in pregnancy, Hibbard[45] demonstrated a markedly increased rate of small-for-dates infants whose mother had low folate levels early in the pregnancy.

Premature delivery

In his study of 100 women at risk for nutritional deficiencies in pregnancy Blot[32] found the duration of pregnancy was shorter than normal in women with low folate but of similar duration in iron deficient and non iron deficient women.

In a previous study, this same group[46] showed that folate supplementation increased pregnancy duration by approximately one week and that the increase in newborn height and weight might be explained by longer gestation.

However, Pritchard et al.[47] examined fetal health and wastage in women who were taking OCs before pregnancy and found no difference from the control population. In a prospective study of 163 pregnant girls under age 16, Daniel and coworkers[48] found no increase in prematurity of infants born to girls with subnormal folates as compared to those of girls with normal folates. None of the patients had third trimester bleeding, abruptio or malformations, although 90.4% of the girls took less than 50% of the recommended diet allowance and 52% of the girls took less than 10% of the recommended levels of folate.

The suggestion that prophylactic folic acid administration would reduce the incidence of pregnancy complications of abortion, abruptio placentae, preterm delivery and congenital malformations has not been confirmed.[49, 50]

In summary, there is much conflicting evidence that maternal folate deficiency is implicated in many pregnancy complications and neonatal pathology. Undoubtedly poor general nutrition is partly responsible for intrauterine growth retardation and prematurity, with attendant risks to the infant.

Effects of OC Usage on Vitamin B_{12} Levels

Prasad et al.[51] found no change in serum vitamin B_{12} levels in users of contraceptive steroids in a high socioeconomic group but there are several reports of reduced serum B_{12} levels in OC users.[52, 53, 55] However, Schilling tests carried out in four subjects with low serum B_{12} levels were normal,[12] indicating that combined OCs did not impair absorption of this compound.

Further, in a study of 20 women taking OCs for two to 60 months, Wertalik et al.[53] showed that though the mean serum B_{12} level was 40% lower than in controls, the mean unsaturated B_{12} binding capacity was unchanged. Further, although 15% of the subjects were clearly in the deficient range ($<100\ \mu\mu g$/ml), one subject having a B_{12} level of 14, and the other 22 $\mu\mu g$/ml, none had anemia or macrocytosis.

Many women will therefore demonstrate lowered serum vitamin B_{12} levels without associated fall in tissue levels or disease. Serum vitamin B_{12} levels in OC users should therefore only be measured if there is a macrocytosis on the peripheral smear or a raised mean corpuscular volume (MCV). Should a lowered serum vitamin B_{12} be found, other causes such as malabsorption syndrome, Crohn's disease, pernicious anemia and decreased intake as in vegans[55] must be considered.

Recommendations

Until more is known of the part played by vitamin B_{12} and folate deficiency in the etiology of pregnancy and neonatal mishaps, the following are recommended:

1. As suggested by Laurence,[57] advice on diet should be part of the health education program at school.
2. Physicians should continue the counselling begun in the schools to all women in the childbearing age group, especially those taking OCs.
3. Periodically all women taking OCs should have their hemoglobin, MCV and a peripheral blood smear examined. A serum B_{12} and RBC folate level should be done only if anemia or macrocytosis is demonstrated.
4. Should the folate or B_{12} level of an OC user be low, other causes than the contraceptive—such as malabsorption, pernicious anemia and usage of other drugs—should be sought and appropriate action taken.
5. Folic acid supplementation should be recommended as soon as a pregnancy is diagnosed.
6. Until more is known about the etiology of neural tube defects, periconceptional folic acid should be considered for all women who have already given birth or aborted fetuses with NTD, since the neural tube closes at eight weeks.
7. Patients with a multiple pregnancy, malabsorption, hemolytic anemia and those using drugs known to be folate antagonists will need greater supplementation.

Finally, I feel two quotations are worthy of note:

"In many cases it seems that misfortune arises when adverse environmental factors act on a constitutionally susceptible mother and fetus".[45]

"It seems improbable that folate deficiency is ever an isolated cause of congential defect in the human being, but it may prove to be one correctable factor involved in malformations of multifactorial origin".[58]

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